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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,965	11/13/2001	Pierre Colas	EGYP 3.0-015	4646

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,965	COLAS ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65,67 and 69-84* is/are pending in the application.

4a) Of the above claim(s) *1-62 and 83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-65,67,77-82 and 84* is/are rejected.

7)☒ Claim(s) *69-76* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 May 2005 and 19 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

2. Applicant's response to the Office Action mailed November 4, 2004 on May 6, 2005 and June 3, 2005 is acknowledged. In addition, the Declaration submitted by Pierre Colas on June 3, 2005 is acknowledged.

Claim Disposition

3. Claims 66 and 68 have been canceled. Claim 84 had been added. Claims 1-65, 67 and 69-84 are pending. Claims 63-82 and 84 are under examination.

Drawing

4. The drawings filed on May 6, 2005 have been accepted by the examiner. Regarding the objection to Figure 1A and B, Figure 2 and Figure 3 based on clarity filed on February 19, 2003, applicant traverses this objection stating that the best images have been submitted (see page 16 of the amendment filed May 6, 2005). This statement is being interpreted as formal drawings have been filed, thus the objection is withdrawn.

Withdrawn-Specification Objections

5. Previous objection to the specification are withdrawn by virtue of submission of an amendment.

Withdrawn-Sequence Compliance

6. Previous compliance issues raised are withdrawn by virtue of submission of an amendment.

Withdrawn-Oath/Declaration Objection

7. Previous objection to the Oath/Declaration is withdrawn by virtue of submission of an amendment.

Claim Objections

8. Previous objection to the claims are withdrawn by virtue of submission of an amendment. However, claims 69-76 are objected to because they depend from a rejected base claim.

Maintained-Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 63-65, 67, 77-82 and 84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for intracellular recognition molecules that are peptide aptamer (such as the sequences disclosed on page 33 and anti-Cdk2 and others listed on page 12 of the specification as well as cited in the prior art), does not reasonably provide enablement for any intracellular recognition molecule (claim 79, for example) or target or TRX-like protein (claim 63 for example). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass a peptide aptamer (intracellular recognition molecule,) and any target bound

to any TRX-like protein as a platform interacting with an unspecified amount of targets (see claim 63 for example); and claims encompass any intracellular recognition molecules and any target bound to any platform having the capacity to interact with the unspecified amount of targets. The specification discloses that using mutagenesis, recognition moieties R, particularly peptide aptamers were prepared (page 8) and a recognition moiety R is any molecule which has the capacity to interact with high specificity and affinity within a cell with a target T (see page 9). However, the only intracellular recognition molecules exemplified are peptide aptamers, for example Cdk2 (see page 12, for example). The platform preferred is thioredoxin, however, the claims are also directed to thioredoxin-like proteins (see claim 63 and page 12 of the specification), however, none is disclosed. It is noted also that paragraph 0059 of the specification disclose that the "thioredoxin-like proteins have at least 18%, preferably at least 40% and most preferably at least 75% homology with the amino acid sequence of *E. coli* thioredoxin over 80 amino acids", which includes an enormous amount of variability, consequently, the desired effect of bonding of the recognition molecule R to the platform may not occur. The specification lacks adequate guidance with regard to the variable T (target) and claims such as claim 79 recite language such as "capacity to" which is not demonstrative of the claimed intracellular recognition molecule R possessing a function, as the term "capacity to" means that the intracellular recognition molecule R may not function as disclosed. Case and point, a human being is capable of leaping off a tall building under certain conditions. In addition, the claims are directed to a recognition molecule that can vary in length, hence may not function as desired, knowing that structural changes can affect the structure-function relationship of a protein.

Note that the intracellular recognition molecule R comprises a recognition domain which is disclosed as "comprising" (see for example claims 72, 73 and 75) or "consists" (see for example claim 64) of peptides having lengths of 10-40, mutations wherein 1-3 amino acid residues are changed or has for example, the amino acid sequence "QVWSLWALGWRWLRRYGWNM" (see claims 72-73, 75 and 64 and page 60 of the specification), which represents open and closed language in association with the structure and there is no indicia as to whether or not the structure once modified will retain the prescribed function or have biological activity. In addition, the preferred peptide is ten to forty amino acids, however, a 20-mer is exemplified. It is also disclosed on page 28 that the peptide can have a mutant having from one to five, preferably one to three amino acid changes with respect to said sequence and there is no indicia as to a conserved region or where in the sequence the modifications will occur and if said modification can be tolerated in the sequence. Due to the large quantity of experimentation necessary to generate the an intracellular recognition molecule comprising a domain that is variable that can interact with any target and to screen same for activity and the lack of guidance/direction provided in the instant specification with regard to the variables in the invention, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are

conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of

unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims as the claims broadly read on intracellular recognition molecule fragments or any target or platform. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification, as the variables are described in vague terms. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct any intracellular recognition molecule with a variable domain having the capacity to specifically interact with any target.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of intracellular recognition molecules and targets which may or may not possess the ability to interact. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level

artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).*

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test all intracellular recognition molecules encompassed in the claims would constitute undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 77-82 are rejected under 35 U.S.C. 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claim 77 is indefinite for the recitation of "each of which being an intracellular recognition molecule" as the claim has an improper sentence structure. It is suggested that the claim is amended to recite "each being an intracellular recognition molecule according to claim 63". See also claim 78.

(b) Claim 79 and the dependent claims hereto remain indefinite for the recitation of "capacity to" as the terms do not necessarily mean that the recognition molecule possess that function as the terms mean that there are times when the function will not occur. Furthermore, it is unclear what else the recognition molecule has the "capacity to" do. It is suggested that the phrase "capacity to" is deleted from the claims.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 79 remain rejected under 35 U.S.C. 102(b) as being anticipated by Brent et al., WO 9602561 A1, 1 February 1996, based on the disclosure that a recognition moiety R is any

molecule which has the capacity to interact with high specificity and affinity within a cell with a target T (see page 9).

Brent et al. teach two proteins capable of interacting, the first protein covalently bonded to a binding moiety which is capable of specifically binding to the DNA-binding-protein recognition site and the second protein covalently bonded also and being conformationally-constrained and measuring the interaction between the two proteins. The peptides taught by Brent et al. are conformationally constrained intracellular peptides. Brent et al. teach a peptide recognition domain comprising a peptide that is identical to the one disclosed in the instant application, randomly generated , see the alignment and a platform for example, thioredoxin (see page 1 of the reference). The peptide taught by Brent et al. consists of 20 amino acids, see the alignment. Although the claim recite functionally language and a K_d value, which is not disclosed by Brent et al., the claims recite the language "capable of" which does not necessarily demonstrate possession of a function and as the composition is taught by Brent et al. the function and K_d value are inherent properties, thus anticipated. Further, claim 79 is anticipated because dimeric and oligomeric recognition molecules are disclosed in the cited prior art since the reference discloses fusion proteins joined together and page 29 of the instant specification discloses a fusion of LexA-Cdk2 which is taught by the reference (page 34). Therefore, the limitations of the claim is met by the reference.

12. Claim 79 remains rejected under 35 U.S.C. 102(b) as being anticipated by Colas et al., Nature, vol. 380, 11 April 1996 (cited on PTO-1449), based on the disclosure that using mutagenesis, recognition moieties R, particularly peptide aptamers were prepared (page 8) and a

recognition moiety R is any molecule which has the capacity to interact with high specificity and affinity within a cell with a target T (see page 9).

Colas et al. teach intracellular reagents that recognize specific targets and inhibit specific network connections. Colas et al. also teach peptide aptamers that bind tightly to their targets with disassociation constants of between 30 and 120nM, see pages 546-550 of the reference. Colas et al. teach the expression of a combinatorial library of constrained 20-residue peptides displayed by the active site loop of *E. coli* thioredoxin and the use of a two-hybrid system to select those that bind human Cdk2. The peptide aptamers of the reference mimic the recognition function and recognized different epitopes on Cdk2 surface. Colas et al. teach that thioredoxin can be used as a scaffold to display such conformationally constrained peptides. The reference discloses that peptides were arbitrarily selected (random peptide). The reference also teaches oligomeric and dimeric intracellular molecules as fusions are disclosed of Cdk2-LexA (as disclosed on page 29 of the instant specification), see claim 79. Although the claims recite functionally language not disclosed in the reference, the language "capable of", does not necessarily demonstrate possession of a function and as the composition is disclosed by the reference, the function is an inherent properties, (see pages 548-550). Therefore, the limitations of the claim is met by this reference.

13. Claims 79-82 remain rejected under 35 U.S.C. 102(b) as being anticipated by Colas et al., TIBTECH, vol. 16, August 1998 (cited on PTO-1449), based on the disclosure that using mutagenesis, recognition moieties R, particularly peptide aptamers were prepared (page 8) and a

recognition moiety R is any molecule which has the capacity to interact with high specificity and affinity within a cell with a target T (see page 9).

Colas et al. describes the isolation of 14 different aptamers (intracellular recognition molecules) by screening transformants by their high specificity of interaction. The reference discloses that the peptide aptamers bind tightly to their target, with a dissociation constant (K_d) ranging between 30 and 120nm. The reference teach the production of conformationally constrained 20-amino acid variable regions that recognized the protein kinase cyclin-dependent kinase-2 (Cdk2), see page 359, left column of the reference. The variable regions were displayed using *E. coli* thioredoxin, used as a platform. The reference also discloses fusion proteins with LexA (page 358, right column), the fusion of two different domains (claim 79, page 355, right column) and two different binding sites (claim 80-82, page 358 right column). Therefore, the limitations of the claims are met by this reference.

Response to Arguments

14. The amendments filed on May 6, 2005 and June 3, 2005 have been considered. Additionally, the Declaration submitted by Pierre Colas has been considered. Note that the formalities issues have been withdrawn, however, rejections remain under 35 U.S.C. 112, first and second paragraphs and 102.

Regarding the rejection under 35 U.S.C. 112, first paragraph, the applicant states on page 18 that claim 63 has been amended to recite that the intracellular recognition molecules are peptide aptamers, however, note that claim 79 was not amended which encompasses any intracellular recognition molecule. Furthermore, claim 63 is problematic with the inclusion of the

language "TRX-like protein" and the remaining issue with regard to the unspecified amount of targets. The response states that TRX platforms are enabled by the instant specification, however, the instant specification does not provide an enabling disclosure of TRX-like protein platforms and a definition provides support but does not provide guidance or exemplification of all that is encompassed in the broad scope of the claim. The definition provided is noted, however, is exemplary not limiting and does not breathe life into the claims. On page 19 of the response it is stated that the Declaration of Pierre Colas shows use of thioredoxin-like platform also provides peptide aptamers according to claim 63. More specifically, it is stated that "human thioredoxin, which is an exemplary thioredoxin-like protein, has been used successfully as a platform according to the present invention". This argument is not persuasive as the claim broadly reads on any platform that is TRX-like protein from any source and the instant specification at paragraph 0059 of the specification states that a TRX-like protein can have 18% homology. A protein having 18% homology may not bind with the intracellular recognition molecule as desired, furthermore, encompasses a large genus of proteins not enabled by the instant specification, nor is sufficient guidance provided with respect to the large genus of proteins. Note that the recognition molecule can be mutated thus the claimed invention is unpredictable with respect to a recognition molecule following modification and a platform following modification binding and specifically interacting with an unspecified amount of targets.

Applicant also state on page 19 that claim 63 is amended to delete the language "having the capacity to", however, note that this language remains in claim 79, thus the rejection remains applicable to the claimed invention. Applicant's state that the Colas Declaration confirms that

peptide aptamers may be selected against a target protein from libraries of peptide aptamers bearing a variable region of 8, 13, 20 or more amino acids, however, as stated in the rejection such is not exemplified in the instant application. Furthermore, the Declaration provided statements, however, no exemplification by way of data was provided. Page 20 of the response indicates that statements made by Dr. Colas in his Declaration regard target proteins such as RasGAP, Fur, Grb2, Raf, ERK1, AKT1 and Hsp70 provides support broad recitation of "target" in the claims, however, this argument is not persuasive as no data was provided to substantiate the claims made in the Declaration. The response states that a Kd value of less than or equal to 5x10-9 M limits the target, however, the claim recites "corresponding to a Kd value of less than or equal to $5x10^{-9}$ M and there is no limitation on the "less than" aspect of the claim, thus a broad range. Applicant's comments made on pages 21-22 are noted, however, are sufficient to obviate this ground of rejection. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. The court is in agreement that the scope of the claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art. The claims of the present invention are broad in scope and do not bear a reasonable correlation with the disclosure provided in the instant specification. Thus, for these reasons and the reasons stated above the rejection remains.

With regard to the art rejections under 35 U.S.C. 102, applicant on pages 23-26 argue that the Kd values of the cited references are outside of the cited range in the claimed invention (see for example claim 63). The rejections have been amended to remove claims reciting the specified

Kd value, however, the rejections remain as independent claim 79 and the claims dependent thereto do not have a Kd value limitation. Thus, for these reasons and the reasons stated above the rejection remains.

Conclusion

15. No claims are presently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr, can be reached at (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Patent Examiner 8/19/05

HOPE ROBINSON
PATENT EXAMINER